Ocular Immunology and Inflammation

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ioii20

Diabetes Mellitus–Associated Uveitis: Clinical Features in a Chilean Series

Pablo E. Sabat , Rodrigo Anguita , Victor Saez , Sergio Morales , Cristhian A. Urzúa , Francisco A. Villarroel & Víctor Velásquez

To cite this article: Pablo E. Sabat , Rodrigo Anguita , Victor Saez , Sergio Morales , Cristhian A. Urzúa , Francisco A. Villarroel & Víctor Velásquez (2020) Diabetes Mellitus–Associated Uveitis: Clinical Features in a Chilean Series, Ocular Immunology and Inflammation, 28:4, 571-574, DOI: 10.1080/09273948.2019.1581226

To link to this article: https://doi.org/10.1080/09273948.2019.1581226

Ocular Immunology & Inflammation, 2020; 28(4): 571–574

ISSN: 0927-3948 print / 1744-5078 online
DOI: 10.1080/09273948.2019.1581226

ORIGINAL ARTICLE

Diabetes Mellitus–Associated Uveitis: Clinical Features in a Chilean Series

Pablo E. Sabat, Rodrigo Anguita, Victor Saez, Sergio Morales, Cristhian A. Urzúa, Francisco A. Villarroel, and Víctor Velásquez

Hospital Del Salvador, Facultad de Medicina, Universidad de Chile, Santiago, Chile

ABSTRACT

Purpose: To describe clinical features of patients with diabetes mellitus-associated uveitis (DMAU).

Methods: Retrospective analysis of clinical records of patients with uveitis and diabetes mellitus (DM) presented in an uveitis referral centre in Chile.

Demographic data, comorbidities, complete ophthalmic examination, and treatments were analyzed.

Results: We found 72 patients with uveitis and DM: 16 with DMAU and poorly regulated DM (22%), 15 with DMAU and well-controlled DM (21%), and 41 with uveitis due to established other causes than DM (57%).

Patients with DMAU in poorly regulated diabetes, presented inflammation of 3–4+ cells in 33%, a fibrinous reaction in 28%, hypopyon in 17% and posterior synechiae in 83%, compared with 5%, 0%, 0%, and 50% in the group with well-controlled DM, respectively ($p < 0.05$).

Most DMAU patients responded well to topical or periocular steroids.

Conclusion: Patients with DMAU with poorly regulated DM present a more severe inflammation compared with patients with DMAU with well-controlled DM.

Keywords: Anterior uveitis, Chilean, Diabetes Mellitus, diabetic retinopathy, iritis, uveitis

The association between anterior uveitis (AU) and diabetes mellitus (DM) was described almost 150 years ago by Noyes.[1] Two decades later, Leber published a series of nine patients with iritis among 36 patients with DM.[2] Ever since, AU associated with diabetes mellitus has been reported in few publications. AU was found in 14 of 37 insulin-dependent diabetic patients with severe autonomic neuropathy compared with one of 143 insulin-dependent patients with no autonomic neuropathy.[3] Rothova et al. described a higher prevalence of DM in patients with AU compared with the healthy population (6% vs 1.4%, respectively). Moreover, this trend was much higher for patients with idiopathic AU when compared to patients with a specific AU etiology (12.5% vs 1.9%, respectively).[4]

In 2017, the International Diabetes Federation has estimated a prevalence of 9.2% of DM for the Chilean population and 8.8% worldwide.[5] This situation, besides the fact that uveitis is the fifth commonest cause of blindness in the developed world[6], provides us an idea about the importance of recognizing this association.

The cause for this association remains unknown, however, an ischemic process, a blood-ocular barrier breakdown, and an immunological dysfunction, have been proposed as possible theories.[3,4,7,8]

MATERIAL AND METHODS

This is a Retrospective observational case-series study of patients with the diagnosis of diabetes mellitus associated uveitis (DMAU).

We reviewed clinical records of patients presenting with uveitis and diabetes mellitus, at the Uveitis Department of Hospital Del Salvador, Santiago, Chile (Chilean National Referral Centre for uveitis). They were classified into three categories: 1. Patients with DMAU with poorly regulated DM (Capillary

Received 12 September 2018; revised 6 February 2019; accepted 7 February 2019
Correspondence: Pablo E. Sabat Hospital Del Salvador, Facultad de Medicina, Universidad de Chile, Santiago, Chile. E-mail: psabat@clc.cl

glycaemia≥300mg/dL and/or HbA1c≥12% [16.5 mmol/L]); 2. Patients with DMAU with well-controlled DM, and; 3 Patients with uveitis with established causes (other than DM).

All patients had a comprehensive workup, infectious and autoimmune causes of uveitis were ruled out in both DMAU groups. These included full blood count, erythrocyte sedimentation rate, C-reactive protein, renal and liver function tests, urine, syphilis serology, chest X-ray, tuberculin skin test or interferon gamma release assay, HLA B27, and ANA. Further tests were requested if clinically indicated, such as angiotensin-converting enzyme, ANCA, ENA, serology for toxoplasmosis, and PCR for herpes virus.

Patients with a secondary cause of uveitis (other than DM) were excluded from further analysis.

The variables analyzed included: age, gender, type of diabetes, comorbidities, initial and final best correct visual acuity (BCVA), intraocular inflammation parameters (AC Cells, flare and vitreous haze), intraocular pressure (IOP), recurrences, complications, glycosylated hemoglobin, treatment type, and duration of inflammation. Intraocular inflammation parameters were graded according to SUN criteria[9], and visual acuity calculations were based on Holladay recommendations.[10]

The data was recorded into an Excel database. Fisher Exact test was used for categorical variables and t student test for continuous variables. P values <0.05 were considered statistically significant. All statistical analyses were performed using GraphPad Prism version 7 (GraphPad Software, San Diego – California).

The research protocol was approved by the Hospital Del Salvador Ethics Committee and fulfilled the Declaration of Helsinki.

RESULTS

We found 72 patients with uveitis and diabetes mellitus out of 1203 uveitis patients. An underlying cause was determined in 41 patients (57%). The most common cause was infectious (herpes virus, toxoplasmosis, and tuberculosis). Thirty-one patients (43%) were diagnosed with DMAU: 16 with poorly regulated DM and 15 with well-controlled DM (Table 1).

The characterization of patients with DMAU is shown in Table 2. In these patients, the average age at diagnosis was 51 years for the poorly controlled DM subjects and 54 for the well-controlled DM patients. Fifty-six percent were male in the first

TABLE 1. Etiologies of uveitis in diabetic patients.

Diabetes Mellitus – Associated Uveitis	With poorly-regulated DM: 16 patients (22%) With well-controlled uveitis: 15 patients (21%)
Established causes, other than DM: 41 patients (57%)	Herpes virus: 8 patients Tuberculosis: 5 patients Secondary to systemic disease (i.e: RA, SLE, RP, Sarcoidosis): 5 patients Toxoplasmosis: 4 patients Sympathetic Ophthalmia: 3 patients White dots syndrome: 2 patients Vogt Koyanagi Harada: 2 patients Related to HLA B27: 2 patients Other: 10 patients

RA: Rheumatoid arthritis; SLE: Systemic Lupus Erythematous; RP: Relapsing Polychondritis; DMAU: Diabetes Mellitus–Associated uveitis

TABLE 2. Diabetes mellitus – associated uveitis: patients characteristics.

	With poorly-regulated DM	With well-controlled DM	P value
Patients/Eyes	16/18	15/20	
Gender	9 male, 7 female	4 male, 11 female	
Age of onset (years), mean ± SD	51 ± 11	54 ± 15	
Type of diabetes	Type 2 in 100%	Type 2 in 12 patients (80%)	
Average duration of DM (years), mean ± SD	11 ± 6	13.3 ± 8.3	p = 0.4
Capillary blood glucose at presentation (mg/dL), mean ± SD	331 ± 76	237 ± 52	p < 0.05
HbA1c (%), mean ± SD	14.2 ± 0.9	7.6 ± 1.15	p < 0.001
Treatment for DM	Insulin (n = 8; 50%) Oral (n = 4; 25%) Diet only (n = 4; 25%)	Insulin (n = 5; 33%) Oral (n = 7; 47%) Diet only (n = 3; 20%)	
Comorbidities of DM	Neuropathy (n = 2; 12.5%) Coronary disease (n = 1; 6.3%)	Neuropathy (n = 1; 6.7%)	

group and only 27% in the latter. All patients in the poorly regulated DM and 80% in the well-controlled group had type 2 DM, with an average duration of diabetes prior to the diagnosis of uveitis of 11 and 13 years, respectively. Half of the patients in the poorly controlled group and one-third in the well-controlled group were on insulin. The capillary blood glucose at presentation averaged 331 mg/dL in the poorly regulated diabetes group and 237 mg/dL in the well-controlled group and the glycosylated hemoglobin was 14.2% and 7.6%, respectively. Few patients in both groups had DM-related comorbidities (neuropathy and coronary disease).

The clinical features of DMAU are shown in Table 3. Patients with DMAU with poorly regulated DM had always anterior uveitis, which was unilateral in 88%. In the well-controlled DM group, the main site of inflammation was anterior in 70%, intermediate in 20% and panuveitis in 10% of the eyes. In both groups, the intraocular pressure averaged 15 mmHg, and the average final best corrected visual acuity was less than 6/30. In terms of inflammation, in the poorly controlled diabetes group, there was a > 2+ cells in 33% of the eyes, an anterior chamber fibrinous reaction in 28%, hypopyon in 17%, and posterior synechiae in 83% of the eyes. The same figures for the well-controlled group were 5%, 0%, 0%, and 50%, respectively ($p < 0.05$ for AC cells >2+, AC fibrinous reaction and posterior synechiae). Vitritis was found in 11% (2 eyes) in the first group, and 35% (7 eyes) in the latter. With respect to diabetic retinopathy, 88% of the patients in the poorly controlled DM, versus 33% in the well-controlled DM group presented any stage of retinopathy ($p < 0.005$). Furthermore, diabetic retinopathy was worse in the first group.

All cases in the DMAU with poorly regulated DM group had a good response to topical treatment (prednisolone acetate 1% given at physician criteria and cycloplegic drops) and only one patient needed a periocular injection of triamcinolone to control the inflammation. The average resolution time was 30.5 ± 16 days and there were no recurrences during the follow-up (4.1 months). In the DMAU with well-controlled DM, in addition to the topical treatment, three patients required systemic prednisone, one mycophenolate mofetil and one a subtenon injection of triamcinolone to control the inflammation.

DISCUSSION

The association between uveitis and diabetes mellitus is well known, and it has been described by several authors since the XIX century.

The cause for this association is not well understood, but several hypotheses have been put forward. Rothova et al[4] proposed an inflammatory process as they found the absence of retinopathy in more than half of the diabetic patients with uveitis, recurrent episodes, and a good response to local steroids. Castagna et al[11] found a significant increase in the CD8+ subset, with CD4 + T cells within normal limits, and a decrease in the CD4+/CD8 ratio in all patients with anterior uveitis and type 1 DM, which could be an expression of the unstable lymphocyte equilibrium. Along the same line, Guy[3] found an association between iritis and severe symptomatic autonomic neuropathy, suggesting a common pathogenic mechanism where insulin antibodies may cross-react with nerve growth factor, which can accumulate in

TABLE 3. DMAU: Clinical features.

	With poorly-regulated DM	With well-controlled DM	P vaule
Patients/Eyes	16/18	15/20	
Site of inflammation	Anterior: 18 eyes (100%)	Anterior: 14 eyes (70%) Intermediate 4 eyes (20%) Panuveitis: 2 eyes (10%)	
Laterality	14 unilateral (88%)	10 unilateral (67%)	p = 0.3
IOP (mm Hg), mean ± SD	15 ± 4.1	15 ± 6.8	p = 0.98
Initial VA (Snellen), mean [min-max]	0.15 [NLP-1.0]	0.23 [NLP-1.0]	
Final VA (Snellen), mean [min-max]	0.1 (HM-0.6)	0.18 [NPL-1.0]	
AC Inflammation grade: Cels > 2+	33% (6/18 eyes)	5% (1/20 eyes)	p < 0.05
AC fibrinous reaction	28% (5/18 eyes)	0%	p < 0.05
Hypopyon	17% (3/18 eyes)	0%	p = 0.096
Posterior synechiae	83% (15/18 eyes)	50% (10/20 eyes)	P < 0.05
Vitritis	11% (2/18 eyes)	35% (7/20 eyes)	
Diabetic Retinopathy	88% Mild = 2 pts Moderate = 7 pts Severe = 2 pts Proliferative = 3 pts	33% Mild = 2 pts Moderate = 2 pts Severe = 0 pts Proliferative = 1 pts	P < 0.005
Time to resolution (days), mean [min-max]	30.5 [7–70]	72 [7–240]	
Follow-up (months)	4.1	9.3	

AC: Anterior chamber

the iris upon sensory or sympathetic denervation. Finally, the blood-ocular barrier breakdown and/or ocular ischemia from pre-existing DM could be an additional pathogenic pathway.[7,8]

In our study, we investigated the clinical features of patients with idiopathic DMAU and divided them into two groups depending on the metabolic status.

We found that uveitis associated with decompensated diabetes mellitus were always anterior and had a much worse inflammation compared with DMAU in patients with well-controlled diabetes. Patients with DMAU with poorly regulated DM presented a statically significant more intense anterior chamber reaction, presence of hypopyon, fibrin and posterior synechiae, and a worse diabetic retinopathy than patients with DMAU with well-controlled DM.

All patients in the DMAU with poorly controlled DM group responded well to topical or periocular steroids within weeks, and no recurrences were seen during the follow-up. The fact that all patients were referred to diabetes specialist upon diagnosis of uveitis and the metabolic control was intensified, may have influenced the absence of recurrences during the follow-up.

Watanabe and cols have recently published similar results in a group of Japanese patients. They found that over 50% of the eyes of patients with diabetic anterior uveitis in a setting of poorly controlled DM, had an anterior chamber inflammation >2+ cells, posterior synechiae, and fibrin with 12% (3 eyes) presenting hypopyon.[12]

Whether the hyperglycemia by itself initiates the inflammation process by inducing ischemia, a breakdown of the blood-ocular barrier or modifying the immune response, or makes a different underlying inflammation process worse, is difficult to assess. We hypothesize the uncontrolled diabetes by itself can drive inflammation through a series of mechanisms that induce a severe anterior chamber inflammation, and thus may be an independent cause of uveitis, however, future research should elucidate this hypothesis.

This work lacks a long-term follow-up for these patients, but to the best of our knowledge, is one of the largest series that depicts the DMAU depending on the metabolic status.

CONCLUSION

Patients with DMAU with uncontrolled diabetes mellitus present a much more severe anterior inflammation even with hypopyon and a fibrinous anterior reaction compared with patients with uveitis, but a well-managed DM. The inflammation responded well to topical or periocular steroid injections in most patients. Several mechanisms have been proposed to explain this association such as ischemia, breakdown of the blood-ocular barrier, or immune response dysfunction.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

ORCID

Pablo E. Sabat http://orcid.org/0000-0002-3243-5741

REFERENCES

1. Noyes HD. Retinitis in glycosuria. *Trans Am Ophthalmol Soc*. 1868;1:71–75.
2. Leber T. Ueber das Vorkommen von Iritis und Iridochorioiditis bei Diabetes mellitus und bei Nephritis nebst Bemerkungen über die Wirkung der Salicylsäure bei inneren Augenentzündungen. *Albr von Græfe's Arch für Ophthalmol*. 1885;31(4):183–202. doi:10.1007/BF01693892.
3. Guy RJC, Richards F, Edmonds ME, Watkins PJ. Diabetic autonomic neuropathy and iritis: an association suggesting an immunological cause. *Br Med J*. 1984. doi:10.1136/bmj.289.6441.343.
4. Rothova A, Meenken C, Michels RP, Kijlstra A. Uveitis and diabetes mellitus. *Am J Ophthalmol*. 1988;106:17–20.
5. IDF diabetes atlas. http://www.diabetesatlas.org/. Accessed August 28, 2018.
6. Suttorp-Schulten MS, Rothova A. The possible impact of uveitis in blindness: a literature survey. *Br J Ophthalmol*. 1996;80:844–848.
7. Oswal KS, Sivaraj RR, Stavrou P, Murray PI. Clinical features of patients with diabetes mellitus presenting with their first episode of uveitis. *Ocul Immunol Inflamm*. 2009;17(6):390–393. doi:10.3109/09273940903200309.
8. Sinha MK, Narayanan R, Chhablani JK. Hypopyon uveitis following panretinal photocoagulation in a diabetic patient. *Semin Ophthalmol*. 2014;29(3):166–168. doi:10.3109/08820538.2013.807846.
9. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. *Am J Ophthalmol*. 2005;140:509–516.
10. Holladay JT. Proper method for calculating average visual acuity. *J Refract Surg*. 1997. doi:10.3928/1081-597X-19970701-16.
11. Castagna I, Famà F, Salmeri G. Anterior uveitis and diabetes mellitus: immunological study. *Ophthalmologica*. 1995;209(2):53–55. doi:10.1159/000310579.
12. Watanabe T, Keino H, Nakayama K, Taki W, Echizen N, Okada AA. Clinical features of patients with diabetic anterior uveitis. *Br J Ophthalmol*. March 2018. bjophthalmol-2017-311453. doi:10.1136/bjophthalmol-2017-311453.